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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/562,762

12/27/2005

Massimo Ferrari

207,385

8763

7590

09/03/2010

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EXAMINER

MABRY, JOHN

ART UNIT

PAPER NUMBER

1625

MAIL DATE

DELIVERY MODE

09/03/2010

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,762	FERRARI ET AL.	
	Examiner	Art Unit	
	JOHN MABRY	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 July 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 26-43 and 47-49 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 26-43 and 47-49 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Response to Applicant's Remarks

Applicant's response on 7/29/10 filed in response to the Office Action dated 3/1/10 has been received and duly noted.

In view of this response, the status of the rejections/objections of record is as follows:

Claim Rejections Maintained

Claim Rejections - 35 USC § 103

Rejection of claims 26-43 and 47-49 is maintained under 35 U.S.C. 103(a) as being unpatentable under 35 U.S.C. 103(a) as being unpatentable over Alt (US 5,512,684) in view of Gandolfi et al (US 4,999,362) and in view of Dorwald (Side Reactions in Organic Synthesis 2005, Wiley-VCH, page 2).

Applicant agrees that the obviousness rejection as disclosed is similar in its initial synthetic pathway to US '684, but differs from known processes in its last steps d1) and d2) which are claimed as follows:

d1) treatment of 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene with alkaline hydroxide in alcohol solvent,
d2) acidification of the product obtained in the preceding stage (d1) with a strong acid, to obtain the corresponding raloxifene salt with the strong acid,
wherein:

– stage (d1) is conducted using methanol as alcohol solvent and excess 30% sodium hydroxide;

– the strong acid used in stage (d2) is concentrated hydrochloric acid and said stage (d2) is conducted directly on the reaction mixture derived from stage (d1) to which equal weight quantities of water and ethyl acetate and finally 37% concentrated hydrochloric acid are added;

– the suspension obtained in stage (d2) is washed with equal weight quantities of water and ethyl acetate.

(a) Applicant argues that Examiner argument in view of Dorwald was not properly used in the rejection in Non-Final Office Action dated 3/1/10 regarding synthetic design. Examiner respectfully disagrees with Applicant's allegations.

As previously argued by Examiner, Alt differs from the instant application in the following ways. Alt isolates the crude product, 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene (VI) prior to converting to desired product

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(I) versus Applicant's did not isolate 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene (VI).

The reference of Dorwald was used to support the fact that it is normal and obvious for organic chemist of ordinary skill to reduce steps in order to achieve the desired product faster and in higher yields.

The Examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art or being "obvious to try". See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007).

Dorwald clearly states that in the design of an organic molecule, a synthetic chemist would need to analyze *"the shortest synthetic strategies which are most likely to give rapid access to the target compound, ideally in high yield and purity"* – see page 2 under 1.2 Synthesis Design.

Again, an artisan of ordinary skill, in this case, an organic chemist, would be motivated to take the prior art of Alt '684 and reduce the step of isolation of 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene (VI) in order to achieve the final product (I) faster and in greater yield and higher purity.

(b) Applicant argues that Examiner argument in view of Gandolfi was not properly used in the rejection in Non-Final Office Action dated 3/1/10. Applicant also states the he “frankly” does not understand why the Gandolfi reference was even used. Examiner respectfully disagrees with Applicant's allegations. Examiner clearly set forth the obviousness of the instant application in view of Gandolfi, but will further address Applicant's concerns.

As previously argued by Examiner, it would be obvious to an artisan of ordinary skill in the art at the time the invention was made to convert the free-form (neutral) compounds of formula (I) and convert said compounds into the corresponding salts for the purposes of obtaining higher purity (decreased side reactions), higher yields and prevention of compound instability. In similar structural compounds, Gandolfi discloses the advantages of obtaining the salts of neutral compounds: increased stability, increased solubility, decreased solubility and ease of crystallization (see column 4, lines 60-63) which contributes to higher purity (decreased side reactions) and higher yields. These salts can be selected from: hydrochlorides and other commonly known and art accepted acids (see column 4, lines 54-59). An artisan of ordinary skill in the art would be highly motivated to combine the compounds of Alt along with the teachings of Gandolfi in order to produce salt compounds of formula I that would lead to higher purity (decreased side reactions), prevention of compound instability and higher yields in the process of synthesizing raloxifene hydrochloride.

The reference of Gandolfi was used to support the fact that it is normal and obvious for organic chemist of ordinary skill to convert the free-form (neutral) compounds of formula (I) and convert said compounds into the corresponding salts for the purposes of obtaining higher purity (decreased side reactions), higher yields and prevention of compound instability. Examiner agrees that they are structural differences between the desired product as claimed and the compounds of Gandolfi. Even in view of the structural difference the desired compound as claimed compared to the Gandolfi compound are secondary cyclic amines which benefits from forming a salt for the purposes of obtaining higher purity (decreased side reactions), higher yields and prevention of compound instability. Additionally, it is reasonable to assume that secondary cyclic amines of Gandolfi and Applicant would have similar characteristics and reactivities. Gandolfi serves as a reference which support Examiner's motivation as to why an ordinary organic chemist would be motivated to make the particular changes.

The Examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art or being "obvious to try". See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007).

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The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that “[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” KSR, 550 U.S. at ___, 82 USPQ2d at 1396. Exemplary rationales that may support a conclusion of obviousness include:

- (A) Combining prior art elements according to known methods to yield predictable results;
- (B) Simple substitution of one known element for another to obtain predictable results;
- (C) Use of known technique to improve similar devices (methods, or products) in the same way;
- (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
- (E) “Obvious to try” – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
- (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;

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(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. See MPEP § 2143 for a discussion of the rationales listed above along with examples illustrating how the cited rationales may be used to support a finding of obviousness. See also MPEP § 2144- §2144.09 for additional guidance regarding support for obviousness determinations.

The aforementioned reasons above describe rationales that support a conclusion of obviousness based upon the KSR International Co. v. Teleflex Inc. decision. At least one of letters (A) - (E) rationale is supported above.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Status of the Claims

Claims 26-43 and 47-49 are pending and rejected.

Claims 1-25 and 44-46 have been cancelled.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John Mabry, PhD whose telephone number is (571) 270-1967. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's primary examiner can be reached at (571) 272-0684, first, or the Examiner's supervisor, Janet Andres, PhD, can be reached at (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/John Mabry/
Examiner
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/Rita J. Desai/
Primary Examiner, Art Unit 1625